REMARKS

I. CLAIM REJECTIONS - 35 U.S.C. § 112, SECOND PARAGRAPH

A. Claims 14, 15, 16, 20, 21, 23-26 and 28

Claims 14, 15, 16, 20, 21, 23-26 and 28 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner states that claim 14 is rejected for being redundant with claim 4; claim 20 is rejected for being redundant with claim 17; claim 23 is rejected for being redundant with claim 18; and claim 24 is rejected for being redundant with claim 19.

Claims 4, 17, 19 and 23 have been cancelled, thus making these rejections moot. The Examiner states in claim 14, the phrase on line 3 "fused to protease followed by" is confusing as the protease is not a fusion protein. Applicants have amended the phrase on line 3 of claim 14 to now recite "operably linked to a serine protease substrate sequence followed by". Applicants respectfully submit that the recitation "operably linked" raises no new issues for consideration and is supported in the Specification on page 5 wherein Applicants state "fuse" means operably linked. Therefore, this rejection should be withdrawn.

The Examiner also states that in claims 1 and 14 the phrase "a protease" should be amended to "said protease". Applicants have amended claim 14 accordingly. Claim 1 has been cancelled, thus making this rejection moot.

The Examiner states that in claims 20 and 25 the phrase on line 7-8 "of protease activity" should be amended to "of said protease activity. Applicants have amended claim 20 accordingly. Claim 25 has been cancelled, thus making this rejection moot.

The Examiner further states in claim 15, the phrase on line 2 "of the serine substrate" is confusing as it is unclear what is meant by "serine substrate". Claim 15 has been amended to now recite "serine protease substrate sequence" to clarify what is meant by serine substrate and consistent with the Examiner's interpretation of the claim.

The Examiner states in claim 15, the phrase on line 2 "or the serine protease substrate" has no antecedent basis. Applicants have amended claim 14 to provide proper antecedent basis for claim 15, thus remedying this rejection.

Additionally, the Examiner states in claims 17, 23, and 28, each on line 2, the phrase "the protease sequence" has no antecedent basis. Claims 17, 23, and 28 have been cancelled, thus making these rejections moot.

The Examiner states in claim 20, lines 3-4 and claim 25, lines 3-4, the phrase "fused to serine protease sequence that encodes a serine protease" is confusing, as the protease is not a fusion protein. Claim 20 has been amended to now recite "operably linked to an \$3/4A serine protease substrate sequence" to further clarify the recitation.

The Examiner states in claims 20, 21, 25, and 26, the phrase "the serine substrate" is confusing. Applicants have amended claims 20-21 to now recite "serine protease substrate" for clarification. Claims 25 and 26 have been cancelled. Therefore, it is respectfully submitted that these rejections should be withdrawn.

II. CLAIM REJECTIONS - 35 U.S.C. § 112, FIRST PARAGRAPH

A. Claims 1-3, 5 and 6

The Examiner has maintained rejection of claims 1-3, 5 and 6 under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner states "the specification does not support the broad scope of claims 1-3, 5 and 6 because the specification does not establish any fluorescent

proteins, other than GFP, that can be used to prepare a fluorescent protease substrate reporter. Furthermore, the specification does not disclose where in any fluorescent protein, other than GFP, the substrate sequence can be inserted with an expectation of successfully producing a fluorescent protease substrate reporter. To determine which fluorescent proteins and where in said proteins the protease substrate can be successfully inserted would require undue experimentation, as the specification fails to provide sufficient guidance to enable one of skill in the art to make and use the full scope of the recited invention."

Claims 1-3, 5 and 6 have been cancelled, thus making this rejection moot.

B. Claims 1-3, 5, 6 and 14-29

The Examiner states the rejection of claims 1-3, 5 and 6 under 35 U.S.C. § 112, first paragraph, as well as new claims 14-29, for insufficient structural written description. The Examiner states the specification fails to sufficiently describe the structural aspects of the genus of fluorescent protease substrates comprised of an N-terminal portion of any fluorescent reporter fused to any protease substrate motive followed by the C-terminal portion of the reporter to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 1-3, 5 and 6 have been cancelled, thus making these rejection moot. Claims 14-15, 18 and 20-21 have been limited to a particular fluorescent protease substrate comprised of an N-terminal portion of a green fluorescent reporter protein operably linked to the C-terminal portion of the reporter, which is adequately described in the specification. Applicants respectfully request this rejection to be withdrawn. All other claims have been cancelled.

C. Claims 25-29

Claims 25-29 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner states "the claim(s) contains subject matter which was not described in the specification." The Examiner alleges the specification fails to disclose a method and recitation of said method and claims 25-29 is deemed new matter.

Although not conceding to the Examiner's rejection, claims 25-29 have been cancelled, thus making this rejection moot.

III. CLAIMS REJECTIONS - 35 U.S.C. § 103

A. Claims 1-7

The Examiner has rejected claims 1-7 under 35 U.S.C. § 103(a) as being unpatentable over Mahajan, et al. in view of Abedi et al. Claims 14 and 15 are also rejected under 35 U.S.C. § 103(a) as being unpatentable over Mahajan in view of Abedi.

The Examiner states that although Mahajan does not teach assaying protease activity using the technique of FACS, Abedi does. Abedi fails to teach the quenching of fluorescents as a result of proteolytic activity; however, Mahajan does. According to the Examiner, it would be obvious to a person of ordinary skill in the art to combine those aspects of Mahajan (a fluorescent fusion protein for measuring protease activity) and Abedi (a fluorescent fusion protein comprised of GFP in a protease substrate motif) to make the instant invention. The Examiner's purported motivation is that the GFP-substrate fusion protein would be smaller than the CFP-peptide-GFP fluorescent substrate taught by Mahajan and the GFP substrate fusion protein would avoid bleed-through background fluorescence, which would occur upon cleavage of the fluorescent substrate taught by Mahajan.

Claims 1-7 have been cancelled. With regard to claims 14 and 15, Applicants respectfully traverse these rejections. Mahajan et al. disclose caspase-mediated proteolysis during programmed cell death or apoptosis. Particularly, the Mahajan reference is looking at the spatial activation of specific members of the caspase family via fluorescence resonance energy transfer (FRET). Abedi discloses a method for construction of peptide or protein fragment libraries using GFP. The libraries contain sequences inserted within the GFP coding region. Abedi further discloses that the properties of the library can be quantitatively monitored and individual members of the library follow using instruments such as the flow sorter, and low and high expressions can be identified. There is no suggestion and/or motivation in the cited references that they be combined, or that they be combined in the manner suggested by the Examiner. Absent such a suggestion, a person skilled in the art who was looking for a solution to the problem of determining whether induction of apoptosis in a cell was followed by a change in the FRET signal of a fluorescent substrate, would hardly be disposed on any objective basis to consider a reference like Abedi, which is not only unconcerned with apoptosis at all, but which shows absolutely no recognition of the detecting quenching by FRET as a result of proteolytic activity. Therefore, claims 14 and 15 are patentably distinct from the combination of Mahajan and Abedi. Applicants respectfully request this rejection be withdrawn.

B. Claims 16-24

Claims 16-24 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Mahajan et al. in view of Abedi et al., and further in view of Martin et al. The Examiner states "Mahajan et al. does not teach analysis of serine protease activity. However, serine proteases, including the NS3/4A protease, were well known in the art. It would have been obvious to a person of ordinary skill in the art to use the method devised from combining of Mahajan et al. and Abedi et

al. as described above, to analyze activity of serine proteases. Motivation to do so is provided by the desire to test for inhibitors of serine protease activity."

Claims 16-17 have been cancelled. The dependencies of claims 18 and 19 have been amended to claim 14. This change in dependency does not expand the scope of these claims. Claims 22-24 have also been cancelled. With regard to claims 20-21, Applicants respectfully traverse this rejection. As stated above, Applicants submit Mahajan et al. disclose caspasemediated proteolysis during programmed cell death or apoptosis. Mahajan is looking at the spatial activation of specific members of the caspase family fluorescence resonance energy transfer (FRET). Abedi discloses a method for construction of peptide or protein fragment libraries using GFP. The libraries contain sequences inserted within the GFP coating region. Abedi further discloses that the properties of the library can be quantitatively monitored and individual members of the library follow using instruments such as the flow sorter, and low and high expressions can be identified. Martin et al. disclose the affinity-selection and biochemical characterization of one particular inhibitor, which is an inhibitor of proteolysis by the NS3 enzyme. Applicants respectfully submit Martin, however, does not relate to Mahajan and Abedi because Martin does not relate to apoptosis in enzymes that are spatially activated as exhibited by Mahajan or constructing peptide or protein fragment libraries using GFP as exhibited by Abedi. Therefore, one of ordinary skill in the art would not likely use such a reference alone or in combination as suggested by the Examiner. Therefore, claims 20-21 are patentably distinct from the combination of Mahajan and Abedi and in further view of Martin. Applicants respectfully request this rejection be withdrawn.

IV. CONCLUSION

This amendment accompanies the filing of a Request for Continued Examination (\$385) and a two month-extension of time (\$210). Please charge Deposit Account No. 26-0084 the amount of \$595.00 for the RCE and extension of time. No other fees or extensions of time are believed to be due in connection with this amendment; however, consider this a request for any extension inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Reconsideration and allowance is respectfully requested.

Respectfully submitted,

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